Tough Call

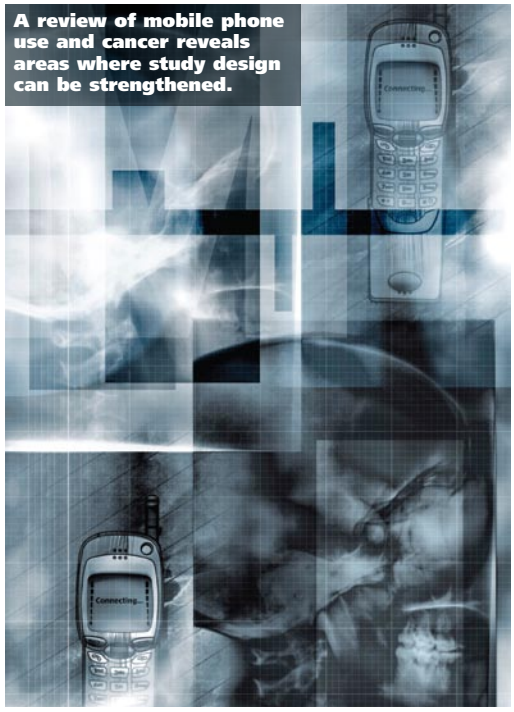
Challenges to Assessing Cancer Effects of Mobile Phone Use

Mobile phone use worldwide has exploded in the past decade, with many countries fast approaching a usage prevalence of 100%. Even as mobile phone use grows exponentially, questions remain regarding the health impact of frequent exposure to the electromagnetic fields (EMFs) associated with mobile phone use. A review of 33 peer-reviewed epidemiologic studies suggests that a number of study design issues may result in an underestimate of the relative risk of brain tumors among mobile phone users [*EHP* 117:316-324; **Kundi**].

Recall bias is a widely cited concern that could lead to biased risk estimates in case–control studies of ipsilateral exposure (i.e., tumors occurred on the same side of the head where the phone was usually held); the review author notes that cancer patients may tend to either attribute their disease to their mobile phone use or to dismiss a relationship between the two. But ipsilateral risks also carry greater biologic plausibility, since one 2008 study showed that nearly 99% of the total electromagnetic energy deposited in the brain is absorbed at the side of the head where the phone is held during calls. According to the author's analysis, more than half of mobile phone users among cases and none among controls would have to incorrectly identify which ear they usually hold their phone to in order to nullify the observed increased risk.

Another source of potential bias concerns the comparison groups used. In the widely cited Interphone study, a case–control study spanning 13 countries, the unexposed group included people who used cordless phones. However, according to the author, cordless and mobile phones users receive about the same EMF exposure, and cordless phones are generally used for longer periods of time than mobile phones. This may help explain why Interphone has consistently reported either no effect or even a protective effect of mobile phone use.

Finally, methods of data acquisition, which have differed substantially between Interphone and other studies, may also introduce bias. Memory performance may be altered in patients with aggressive gliomas, malignant brain tumors that have been associated with mobile phone use in some studies. The author also suggests that exposure assessment may be biased if conducted by phone interviews (as in the Interphone study) compared with the mailed questionnaire method.



A review of mobile phone use and cancer reveals areas where study design can be strengthened.

According to the review author, results of the research to date suggest an association between mobile phone use and glioma risk that falls in the range of magnitude delineated for passive smoking and lung cancer. Confidence in a causal relationship is bolstered by two key findings: longer latencies are associated with higher risk estimates, and living in a rural area—where mobile phones typically radiate at higher intensities—also is associated with elevated risk. Even a modest cancer risk could have major public health implications because of the vast number of mobile phone users. On the other hand, as this review points out, the individual risk perspective is less dramatic: in industrialized countries, the prevailing life-time brain tumor risk is 4–8 per 1,000, and thus individual risk is still low if mobile phone use increases the risk even 50% to 6–12 per 1,000. –M. Nathaniel Mead

Protein Baggage

Toxicity of Organotin Tied to Proteasome Interference

Organotins have been widely used as agricultural pesticides, antifungal agents, polyvinyl chloride stabilizers, industrial catalysts, and antifouling additives in boat paints. These tin-based chemicals, which have been detected in various environmental media, are lipophilic and thus capable of becoming increasingly concentrated as they pass up the food chain. A new study suggests that the toxic effects of organotins on living cells are mediated in part by inhibiting the function of the proteasome, a molecular structure that degrades unneeded or damaged proteins [*EHP* 117:379–386; **Shi et al.**].

In eukaryotic organisms (animals, plants, fungi, algae, and plankton), more than 80% of intracellular proteins are degraded through the proteasome-mediated pathway. By interfering with proteasome function, organotins enable proteins to accumulate inappropriately. Because normal immune function and many cellular processes depend on the proteasome pathway, the organotin–proteasome interaction could help explain some of the adverse health effects of organotins—notably endocrine disruption, infertility, and immune dysfunction—that have been observed in wildlife and in animal studies. In addition, human exposure to organotins has been proposed as a possible risk factor for cancer (by inhibiting the cytotoxic function of natural killer cells), neurotoxicity, obesity, allergies, asthma, and altered reproductive development.

The researchers provide several lines of evidence suggesting that triphenyltin (TPT), a common organotin, binds to and blocks the activity of the proteasome by irreversibly inhibiting its protein-degrading activity. TPT was shown to have greater potency in this regard than seven other organotins examined by the authors. The investigators deduced that the tin present in TPT interacts with the N-terminal threonine of the proteasomal β5 subunit, possibly providing a specific target for organotins. Organotins have long been known to induce necrosis; the authors propose this may occur through caspase-dependent, DNA damage–independent cell death. In addition, the researchers assert that organotins most likely kill cells via a p53-independent pathway.

The new findings suggest that other previously identified potential targets of organotins, such as the transcription factor NFκB and the pro-apoptotic protein Bax, might be downstream of proteasome inhibition. The investigators further posit that inhibition of aromatase activity observed in organotin-exposed humans and animals—an effect linked to altered reproductive development—may be due to proteasome inhibition because such inhibition causes up-regulation of factors that suppress transcription of the *hCYP19*/aromatase gene. –M. Nathaniel Mead

Corbis

From Dust to Blood

Studies Predict Lead Intake in Children

Lead concentrations in U.S. children's blood have decreased markedly in recent decades, thanks largely to lower industrial emissions, voluntary elimination of lead solder in food cans, and legislation barring lead from gasoline and new paint. The main source of lead exposure for today's children is deteriorating lead-based paint, which contributes to lead-laden dust in older homes. Two studies, the first of their kind to use nationally representative data from U.S. homes, predict how varying degrees of lead contamination of floor and windowsill dust may affect the blood lead levels of resident children [***EHP* 117:461–467; Gaitens et al.**; ***EHP* 117:468–474; Dixon et al.**].

Despite reductions in child blood lead levels, the U.S. Centers for Disease Control and Prevention (CDC) estimates on the basis of 1999–2002 data that some 310,000 children still have levels above the agency's threshold of concern, 10 µg/dL. Such children are at increased risk for cognitive impairment and behavioral problems. Mounting evidence [e.g., *EHP* 116:243–248 (2008)] has linked even lower blood lead levels with adverse effects.

The current studies examined lead- and housing-related data for a nationally representative group of 2,155 children aged 1–5 years, drawn from the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2004. In addition to blood lead data, dust samples had been collected from floors and windowsills in the children's homes and analyzed for lead content. The study by Gaitens et al. showed that dust lead levels in the great majority of homes met or exceeded federal standards: just 0.16% of homes failed the standard for floors of 40 µg/ft^2, and 4.0% failed the standard for windowsills of 250 µg/ft^2. Income, race/ethnicity, floor condition, windowsill dust lead content, year of home construction, recent renovation, smoking, and survey year all were significant predictors of floor dust lead loading, which was more predictive than windowsill dust lead of elevated blood lead in residents.

Dixon et al. examined blood lead levels for the same 2,155 children and used a linear regression model to predict children's blood lead given a range of floor dust lead concentrations from very low (0.25 µg/ft^2) up to the federal standard of 40 µg/ft^2. Based on logistic regression models, the authors estimated that among children living in pre-1978 homes with floor dust lead levels of 12 µg/ft^2, 4.6% would have a blood lead level of at least 10 µg/dL, whereas 27% would have a level of at least 5 µg/dL. Because the blood lead and dust lead levels observed in the NHANES data set were relatively low, the researchers verified the models' predictive capacity by analyzing data from three high-risk populations with higher levels of both blood lead and floor dust lead than those observed in NHANES.

The studies indicate that most U.S. homes already meet federal standards for floor and windowsill dust lead levels, but also suggest that further tightening of the standards would afford greater protection for today's children. However, although data for both studies came from a nationally representative sample of children, the homes may not necessarily represent the U.S. housing stock. The authors cite the need for an integrated health and housing survey that is representative of both the population and the housing stock, similar to surveys recently conducted in Europe. –Rebecca Kessler

Synergy for Salmon

Study Spawns Insight into Pesticide Mixtures

Years of habitat degradation, overfishing, hatchery practices, and dam building have left U.S. wild salmon populations struggling to recuperate. Another potential threat that hasn't been considered is the combined impact of multiple pesticides that are found in waterways. In a study of various pesticide mixtures, researchers found the presence of adverse effects that were synergistic, not just the additive effects anticipated under current regulations [***EHP* 117:348–353; Laetz et al.**]. In light of the current findings, mixtures that have been considered relatively safe may pose more of a hazard to wildlife than was previously thought.

The researchers evaluated the effects of diazinon, malathion, chlorpyrifos, carbaryl, and carbofuran—which are among the most extensively used pesticides in California and the Pacific Northwest—in the brains of juvenile coho salmon. These chemicals inhibit the enzyme acetylcholinesterase (AChE), resulting in an accumulation of acetylcholine, which in turn can affect behavior and, ultimately, survival.

For each of 10 pairings of the 5 pesticides, concentrations were designed to elicit AChE reductions of 10%, 29%, or 50% (assuming the chemicals acted additively) for a total of 30 possible exposures. Other fish were exposed to single pesticides; none were tested for combinations of 3 or more chemicals.

This map shows the overlap between the range of endangered salmon species (gray areas) and study areas where multiple pesticides have been measured in surface waters (dashed lines).

Nearly every pairing inhibited AChE activity after the salmon were exposed over a 96-hour period. Synergistic inhibition was observed in 20 of the 30 combinations, producing anywhere from about 20% stronger inhibition than predicted by additive activity alone to more than 90% inhibition in 5 combinations. For 3 combinations, the salmon died within 24 hours. In contrast, there were no deaths among fish exposed to individual pesticides only.

The synergistic effects were almost uniformly more pronounced as the exposure increased. Nonetheless, even at lower, more environmentally relevant concentrations, the synergistic effects were significant for 4 of the 10 pairings. For some chemical combinations, the data suggest synergistic effects are possible at concentrations below the lowest levels used in the study.

In a 2007 study, more than 90% of water samples from urban, agricultural, and mixed-use streams contained 2 or more pesticides, residue from more than 1.2 billion pounds of pesticides applied each year. The investigators conclude that more studies of pesticide combinations must be done on live fish—especially since their results weren't predicted by *in vitro* studies—and that more work is needed to determine the lower bounds for pesticide interactions. Furthermore, if synergistic effects occur at concentrations found in habitats supporting salmon stocks, which often include species designated as threatened or endangered, regulators may need to consider multichemical effects when setting exposure standards. –Bob Weinhold

Laetz et al.